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REVIEW

Impact of pegloticase on patient outcomes in refractory gout: current perspectives

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Rita N Cunha[1]
Renata Aguiar[1]
Filipa Farinha[2]

[1]Rheumatology Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; [2]Centre for Rheumatology, University College London, London, UK

Abstract: Gout is currently the most frequent cause of inflammatory arthritis worldwide and is responsible for poor health-related quality of life and loss of work productivity. It is caused by high levels of serum urate, leading to the deposition of monosodium urate crystals in joints and soft tissues. This condition is associated with acute flares and, if untreated or refractory, chronic and potentially destructive arthritis and tophi formation. Pegloticase is a recombinant, pegylated uricase used in the treatment of gout patients who fail conventional urate-lowering therapy. In this review, we discuss the impact of pegloticase on patient outcomes in refractory gout. We analyze different parameters, such as plasma uric acid concentration, frequency of flares, tophi reduction, pain, function, quality of life, and safety.

Keywords: gout, urate-lowering therapy, pegloticase, patient outcomes

Background

Although its prevalence is highly variable in different regions, gout is currently the most frequent cause of inflammatory arthritis worldwide. Several factors, such as genetic background, age, gender, dietary factors, comorbid conditions, and medications, modify the risk for the disease.[1]

Gout is caused by high levels of serum urate due to its overproduction (10%), underexcretion (90%), or both,[2] leading to the deposition of monosodium urate crystals in joints and soft tissues, which initially cause intermittent attacks of acute arthritis. In the absence of effective treatment, the disease progresses into a form of chronic and potentially destructive arthritis and tophi formation.[3] Patients with gout describe severe pain in the affected joints, which negatively impacts their quality of life (QoL), particularly physical functioning and sleep.[4] As prevalence increases, refractory cases also become more frequent and are responsible for important loss of work productivity.[5]

Long-term management of gout aims to reduce serum urate levels (SUAs) to <6 mg/dL – or to <5 mg/dL in patients with tophaceous gout, severe arthropathy, or recurrent attacks.[6,7] Pharmacological treatment includes 3 classes of drugs: xanthine oxidase inhibitors (XOIs), which inhibit urate synthesis – allopurinol and febuxostat; uricosurics – lesinurad, sulfinpyrazone, probenecid (and benzbromarone in some countries); and the enzyme uricase – pegloticase. XOIs are the mainstay of gout treatment. Allopurinol has long been the first-line urate-lowering therapy (ULT), considering its efficacy, safety profile, wide availability, and low cost.[8] However, the small risk of severe cutaneous adverse reactions, drug interactions such as with

Correspondence: Rita N Cunha
Rheumatology Department, Centro Hospitalar do Baixo Vouga, Avenida Doutor Artur Ravara, 3810-193 Aveiro, Portugal
Tel +351 2 3437 8300
Email rita__novais91@hotmail.com

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azathioprine, and the major renal excretion, requiring dose adjustment, limit allopurinol use in some patients. Severe cutaneous hypersensitivity reactions are a rare side effect and are more common among patients of specific Asian backgrounds who are positive for the human leukocyte antigen B*5801 allele.[9,10] Febuxostat has comparable efficacy to allopurinol in reducing serum urate, with lower risk of hypersensitivity reactions.[11,12] In fact, a network meta-analysis comparing different ULTs found febuxostat to be the most efficacious and safe.[13] However, due to its higher cost, it is often reserved for patients in whom allopurinol was inefficient, contraindicated, or caused adverse reactions.[14] Uricosurics decrease serum urate by inhibiting renal reabsorption and therefore increasing renal excretion; they are a useful option for patients who cannot tolerate XOIs or in association with them.[15,16]

Uricase is an enzyme present in most non-primate mammals that converts urate into the more soluble product allantoin, which is absent in humans. Rasburicase, an uricase derived from *Aspergillus flavus*, was used to prevent tumor lysis syndrome in patients with hematological malignancies.[17] However, its short half-life, potential immunogenicity, and limited number of studies supporting its use in gout patients[18] limit its use in such setting. Pegloticase is a porcine recombinant, polyethylene glycol-conjugated uricase; it was approved by the US Food and Drug Administration in 2010 and by the European Medicines Agency in 2013 (although the marketing authorization for pegloticase in the European Union has been withdrawn in June 2016 at the request of the marketing-authorization holder, for commercial reasons) for the treatment of patients with severe gout who fail conventional ULT. Both the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) recommendations advise the use of pegloticase in patients with severe gout and impaired QoL, in whom the disease cannot be properly treated with any other available drug, or combination, at the maximal dosage.[6,7]

Our objective is to review the available data on the impact of pegloticase on patient outcomes.

Methods

We performed a literature search on PubMed, using the mesh terms "pegloticase" [supplementary concept] OR pegloticase, without applying any filters. Selection criteria included both observational studies and clinical trials evaluating outcomes of treatment with pegloticase in patients with gout. We excluded case reports, studies in animal models, and articles published in languages other than English, Portuguese, Spanish, or French.

Results

Our search retrieved 120 articles. After reading the title and/or abstract, 16 articles were selected for full text reading. In the end, 7 articles were included in this review (Table 1). Articles excluded were either reviews, sub-analyses of the studies already included, case reports, and animal studies.

We now present the results for the following outcomes: plasma uric acid concentration; frequency of flares; pain, function, and QoL; tophi resolution and safety.

Plasma uric acid concentration

In 2006, Ganson et al, from the Duke University Medical Center in North Carolina, published the first open-label phase I trial to investigate efficacy and safety of pegloticase, including immunogenicity. In this trial, a single subcutaneous injection of 4–24 mg of the drug was administered to 13 patients with refractory gout (overall plasma urate concentration [pUAc] 11.3±2.1 mg/dL, after 2-week allopurinol washout).[19] Outcome efficacy was assessed by the magnitude of decrease in pUAc. By day 7 after injection, this had declined by an average of 8 mg/dL and had normalized in 11 subjects. At day 21 following injection, pUAc remained 6 mg/dL or less in patients receiving 8, 12, and 24 mg of pegloticase.

One year later, the same group published another phase I trial, evaluating pharmacokinetics and safety of intravenous pegloticase.[20] Single infusions (at doses ranging from 0.5 to 12 mg) were administered to 24 patients (6 cohorts of 4 patients each). Parameters such as plasma uricase activity (pUox), pUAc, and the uric acid-to-creatinine ratio (Uac:Cr) in urine were evaluated for 21 days after administration. Adverse events (AEs) and the IgG antibody response to pegloticase were monitored for 35 days. Prior to infusion, the mean pUAc in all patients in this trial was 10.9±0.5 mg/dL. Doses of 4–12 mg allowed a greater reduction of pUAc from a mean ± SD value of 11.1±0.6 to 1.0±0.5 mg/dL within 24–48 hours. After day 21, the mean pUAc for all 6 dose cohorts remained 2.0 mg/dL, or 9.8 mg/dL below baseline.

A multicenter, open-label, randomized, parallel-group phase II trial evaluated the efficacy of multiple doses and dose regimens of pegloticase, administered by IV infusion in patients with refractory gout, for 12–14 weeks.[21] Patients were randomized into 1 of 4 pegloticase treatment groups: 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks, and 12 mg every 4 weeks. Primary efficacy endpoint was the percentage of treatment responders, defined as a pUAc

Table 1 Summary of main studies analyzing the outcomes of administration of pegloticase in patients with gout

Study	Population	Intervention	Outcome	Results
Ganson et al (2006)[19] Open-label phase I trial	13 patients with refractory gout	Pegloticase as a single subcutaneous injection (4–24 mg)	✓pUox ✓pUAc ✓Antibody against pegloticase ✓AEs	**Plasma uricase activity:** ✓8 subjects: pUox still measurable at 21 days after injection ✓5 subjects: pUox not detected beyond 10 days after injection **Plasma urate concentration:** ✓7 days after injection: declined by an average of about 8 mg/dL and normalized in 11 subjects ✓21 days following injection: pUAc remained 6 mg/dL or less in patients receiving 8, 12, and 24 mg of pegloticase ✓Inverse relationship between simultaneously measured pUox and pUAc ✓5 subjects with antibody against pegloticase
Sundy et al (2007)[20] Open-label phase I trial	24 patients with refractory gout	Six cohorts of 4 patients receiving single intravenous infusions of 0.5, 1, 2, 4, 8, or 12 mg of pegloticase	✓pUox ✓pUAc ✓Uac:Cr in urine ✓IgG antibody response to pegloticase ✓AEs	✓Doses of 4–12 mg: pUAc fell from 11.1±0.6 to 1.0±0.5 mg/dL ✓Maximum pUox linearly related to the IV dose of pegloticase ✓Uac:Cr ratio in urine fell in parallel with the pUAc ✓9 patients with IgG antibodies to pegloticase ✓20 gout flares in 14 study patients
Sundy et al (2008)[21] Open-label randomized phase II trial	41 patients with refractory gout	12–14-week treatment with pegloticase 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks, or 12 mg every 4 weeks	✓pUox ✓pUAc ✓Anti-pegloticase antibodies ✓Pharmacokinetic parameters ✓AEs	✓Rapid reduction (within 6 hours) in pUAc to ≤6 mg/dL in all treatment groups ✓Sustained reduction in the 8 and 12 mg dosage groups ✓Biggest reduction in 8 mg every 2 weeks group ✓31 of 41 patients developed anti-pegloticase antibodies ✓Gout flares occurred in 88% of the patients
Sundy et al (2011)[22] Two replicate RCTs	225 patients with refractory gout	Three groups: pegloticase 8 mg at each infusion (biweekly treatment group), pegloticase 8 mg alternating with placebo (monthly group), or placebo (placebo group). Duration: 6 months	**Primary efficacy endpoint:** ✓Proportion of pUAc responders **Secondary outcomes:** ✓Tophus resolution ✓Reductions in the proportion of patients with gout flare and in the number of flares per patient during months 1–3 and 4–6 of the trial ✓Reductions in TJC and SJC ✓Patient-reported changes in pain, physical function (HAQ-DI), and health-related quality of life (SF-36)	**Proportion of pUAc responders:** greater in each pegloticase group than the placebo group (P≤0.01) **Tophus resolution**: 40% of patients in biweekly pegloticase group (P=0.02), 21% of patients in monthly pegloticase group (P=0.020), and 7% of placebo group **Incidence of gout flares and number of flares:** ✓During 1–3 months: higher for biweekly pegloticase group (P=0.01) and monthly pegloticase group (P>0.01) compared with the placebo group ✓During 4–6 months: significant reductions in the proportion of patients with gout flare in the biweekly treatment group (41%) vs the placebo group (67%) (P<0.007). Fewer flares per patient in biweekly pegloticase group (difference not significant) (P=0.32). **TJC and SJC:** reductions in patients treated with pegloticase compared with placebo, but only differences in TJC were statistically significant (P=0.01) **Quality of life:** ✓**Biweekly treatment:** statistically significant mean improvements in PtGA pain (P=0.01), HAQ-DI (P<0.03), and baseline SF-36 ✓**Monthly pegloticase group:** improvements in PtGA, HAQ-DI (P<0.001), and PCS scores (P<0.01) ✓Statistically significant improvements reported in 6 of 8 SF-36 domains with biweekly pegloticase and 3 of 8 domains with monthly pegloticase

(*Continued*)

Table 1 (*Continued*)

Study	Population	Intervention	Outcome	Results
Becker et al (2013)[23] OLE of RCTs	149 patients who completed either of 2 replicate RCTs	Pegloticase 8 mg every 2 weeks or every 4 weeks during 25±11 months	**Primary outcome:** ✓Safety (number of gout flares and IRs) **Secondary outcomes:** ✓Urate-lowering (pUAc and SUA levels) and clinical efficacy (gout flares and tophus burden)	**Primary outcome:** ✓Gout flares and IRs: least common in patients with a sustained urate-lowering response to treatment and in biweekly group **Secondary outcomes:** ✓Most responders to biweekly and monthly pegloticase in the RCTs maintained SUA <6 mg/dL ✓Tophus burden: at the final visit, 60% of patients with complete response (reported with more detail in Baraf et al, 2013)[24]
Hershfield et al (2014)[25] Open-label phase II trial	30 patients with refractory gout, including • 7 organ transplant recipients • 3 patients who had received pegloticase in previous clinical trials	Five infusions of pegloticase (8 mg) at 3-week intervals	✓pUox ✓pUAc ✓Clinical response ✓Safety ✓Antibody response to pegloticase	✓pUAc rapidly normalized in all treated patients ✓remained <6 mg/dL in 17 persistent responders ✓hyperuricemia recurred in 12 transient responders ✓Improvement of symptoms after 5 infusions ✓Most common AEs: gout flares (90%) and infusion reactions (43%) ✓Among 27 pegloticase-naïve patients, antibodies to pegloticase developed in ✓1 of 7 (14%) organ transplant recipients ✓9 of 20 non-recipients
Araujo et al (2015)[26] Prospective observational study	Ten patients with refractory gout	Pegloticase 8 mg intravenously every 2 weeks, during 13.3 weeks	Resolution of tophi	✓Reduction of tophi in all patients ✓71.40% reduction in volume of tophi ✓94.76% volume reduction in responders; 47.97% reduction in partial responders

Abbreviations: AEs, adverse events; HAQ-DI, Health Assessment Questionnaire-Disability Index; IgG, immunoglobulin G; IR, infusion-related reaction; IV, intravenous; OLE, open-label extension; PCS, physical component summary; PtGA, patient global assessment of disease activity; pUAc, plasma urate concentration; pUox, plasma uricase activity; RCTs, randomized controlled trials; SUA, serum urate level; SF-36, Medical Outcomes Study Short form-36; SJC, swollen joint count; TJC, tender joint count; Uac:Cr, uric acid-to-creatinine ratio.

of 6 mg/dL for at least 80% of the study period. Secondary efficacy endpoints were the percentage of time without hyperuricemia, mean plasma urate, and the relative reduction of the plasma urate level from baseline. A rapid reduction (within 6 hours) in the mean plasma urate levels to ≤6 mg/dL was observed in all treatment groups. This reduction was sustained over the entire study period (to 28 days following the last study dose), except for the 4 mg every 2 weeks group. The greatest reduction was observed in the 8 mg every 2 weeks group. Mean pUAc during treatment was 4.12±2.02 mg/dL in the 4 mg every 2 weeks group, 1.42±2.06 mg/dL in the 8 mg every 2 weeks group, 3.21±2.26 mg/dL in the 8 mg every 4 weeks group, and 3.09±2.46 mg/dL in the 12 mg every 4 weeks group.

In 2011, the results from 2 replicate 6-month, randomized, double-blind, placebo-controlled, multicenter (56 sites from US, Canada, and Mexico), phase III trials were published. These randomized controlled trials (RCTs) included 225 adult patients with chronic gout refractory to conventional therapy and gave the most conclusive data about efficacy and tolerability of pegloticase.[22] Patients were randomized into 3 groups: pegloticase 8 mg at each infusion (biweekly treatment group), pegloticase 8 mg alternating with placebo (monthly group), or placebo (placebo group). The primary efficacy endpoint was the proportion of responders in each pegloticase treatment group. It was defined as a pUAc <6.0 mg/dL for 80% of the time or longer during both months 3 and 6. Secondary endpoints included tophus resolution, reductions in the proportion of patients with gout flares and in the number of flares per patient during months 1–3 and 4–6 of the trial, reductions in tender and swollen joint counts, and patient changes in pain, physical function, and QoL. The proportion of pUAc responders in each pegloticase group (42% [95% CI: 32–54] in the

biweekly treatment group; 35% [95% CI: 24–46] in the monthly treatment group) was greater than for the placebo group, which had nil responders ($P \leq 0.01$). The responders maintained pUAc substantially below 6.0 mg/dL for the entire 6-month treatment period.

A 30-month open-label extension (OLE) study enrolled 151 patients who had completed either of the 2 RCTs (57 [97%] patients from the biweekly pegloticase group, 55 [93%] from the monthly treatment group, and all 39 patients from the placebo group). It assessed the long-term safety up to 3 years of treatment with pegloticase in patients with refractory chronic gout.[23] Patients received pegloticase 8 mg every 2 weeks (biweekly) or every 4 weeks (monthly). The primary outcome was safety, evaluated by the number of gout flares and infusion-related reactions (IRs). Secondary outcomes included urate-lowering (measured by pUAc levels) and clinical efficacy (assessed by gout flares and tophi burden). In the end, 149 patients received a mean of 28 pegloticase infusions (SD=18) and were followed for a mean of 25 months (SD=11). Most responders to biweekly and monthly pegloticase in the RCTs maintained SUA <6 mg/dL throughout the OLE study. In fact, 55% of all patients achieved the target range SUA at week 25 of the OLE study. On the contrary, in patients who lost urate-lowering efficacy, this happened within the first months of treatment in the RCTs, and urate levels for these patients remained <6 mg/dL for the duration of the OLE study.

Another open-label phase II trial was conducted posteriorly, at the Duke University Medical Center, and published in 2013.[24] The objective was to evaluate dosing of intravenous administration of 8 mg of pegloticase, every 3 weeks, and to further investigate antibody response to pegloticase. This administration regime was consistent with pharmacokinetics and was effective in controlling hyperuricemia in 17 of 30 patients (57%).

Frequency of flares

In the study by Ganson et al, 6 subjects (46%) developed gout flares during the 21-day period of observation after injection of pegloticase.[19]

In the second phase I trial, the most common AE was, again, acute gout flare (20 flares in 14 study patients, from a total of 24 patients).[20] The mean time to onset of an initial gout flare was 13.6 days. No relationship was observed between the pegloticase dose and the time to an initial gout flare.

In the phase II trial by Sundy et al, 88% of patients reported one or more flares of gout during the study (86% in the 4 mg every 2 weeks group; 63% in the 8 mg every 2 weeks group; 92% in the 8 mg every 4 weeks group; and 100% in the 12 mg every 4 weeks group).[21]

The results from 2 phase III trials demonstrated that during 1–3 months, both the incidence of gout flares and the number of flares per patient were higher for pegloticase-treated patients compared with the placebo group.[22] Conversely, during 4–6 months, significant reductions were seen in the proportion of patients with gout flare in the biweekly treatment group (41%) vs the placebo group (67%) ($P<0.007$).

In the OLE study, gout flares occurred in 71% of patients, with the highest flare rates occurring during the first 3-month period.[23] The number of flares diminished with continued treatment and these were less common in patients with a sustained urate-lowering response to treatment and those receiving biweekly pegloticase treatment.

Pain, function, and QoL

The efficacy of pegloticase on pain, physical function, and health-related quality of life (HRQoL) in patients with refractory chronic gout was evaluated as a secondary outcome in the 2 phase III trials.[22] The outcome was measured at baseline and at 13, 19, and 25 weeks. Patient global assessment of disease activity (PtGA) and pain were analyzed using a 100-mm visual analogical scale, physical function by Health Assessment Questionnaire-Disability Index (HAQ-DI), and HRQoL by Medical Outcomes Study Short form-36 (SF-36). SF-36 includes 8 domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH), which are gathered into physical component summary (PCS) and mental component summary (MCS) scores. For each outcome, the minimum clinically important difference (MCID), representing the level of improvement that is perceptible to patients, was defined as ≥10 points on a 100-mm visual analogical scale. Patients who received pegloticase reported significant improvements in physical function and QoL compared with placebo. Additionally, in the biweekly pegloticase group, there were improvements in patient-reported pain, HAQ-DI scores, and SF-36 PCS scores.[22]

Strand et al performed a more detailed analysis of patient-reported outcomes using the evidence from phase III RCTs, by combining values for each treatment group (biweekly treatment, monthly treatment, and placebo) at week 25.[27] Patients receiving pegloticase reported significant improvements in physical function and HRQoL. At week 25, the percentage of patients with clinically important improve-

ments in the biweekly treatment group was 54% for PtGA (vs 29% in the placebo group, P=0.03), 55% for pain (vs 27%, P=0.01), 45% for HAQ-DI (vs 16%, P<0.03), and 64% for SF-36 PCS scores (vs 29%, P<0.01). Patients receiving monthly pegloticase also presented significant improvements in PtGA, HAQ-DI, and PCS scores. Statistically (and clinically) significant improvements were reported in 6 of 8 SF-36 domains (PF, RP, BP, GH, VT, SF) with biweekly pegloticase and 3 of 8 domains (PF, RP, BP) with monthly pegloticase.[27]

Tophi resolution

Tophi resolution was evaluated as a secondary endpoint in the RCTs[22] and in the OLE study,[23] and the results were presented with more detail in a separate publication.[24] The measures used to evaluate this endpoint were tophus complete response (CR) and target tophus CR (TT-CR). CR was defined as complete resolution of at least one tophus without development of new tophi or progressive enlargement of any other tophus. TT-CR was defined as a 100% decrease in the area of the tophus and is reported as the number or proportion of all baseline tophi with CR at the specific study visit. These measures were obtained using Computer-Assisted Photographic Evaluation in Rheumatology (CAPER) methodology. Photographs of the hands and feet were taken at baseline, repeated at weeks 13, 19, and 25 of the RCTs, and at weeks 13, 25, 53, 77, and 101 of the OLE study. CR was compared for each pegloticase dosing group vs the placebo group and according to the patient's pUA response. Among 212 patients randomized in RCTs, 155 (73%) had one or more tophi at baseline. At the end of the RCTs, tophus resolution was reported for 40% of patients in biweekly pegloticase group (P=0.002 vs placebo), 21% of patients in monthly pegloticase group (P=0.02), and 7% of those treated with placebo. In OLE study, a total of 113 patients with tophi at the baseline were included. Tophus CR and TT-CR continued to increase during OLE study, reaching 70% (39/56) of patients and 55% (132/238) of target tophi after 1 year of treatment in patients receiving pegloticase during both the RCTs and OLE.[24] At the final visit, overall tophus CR was achieved in 56 (60%) of 94 patients and the TT-CR in 207 (53%) of target tophus. In this period, responders to pegloticase in the RCTs had a higher TT-CR than non-responders (79% vs 27%).

Araujo et al conducted a prospective observational study to investigate the effect of pegloticase on resolution of tophi in patients with refractory gout.[26] Ten patients (7 males and 3 females) were enrolled in this study. Pegloticase 8 mg was administered intravenously every 2 weeks, after all other uric acid lowering therapy was stopped. Tophus deposits were evaluated by dual-energy CT scans of hands and feet before the first pegloticase infusion and after the last infusion. SUA levels were obtained before and after each infusion. Five patients were classified as responders (SUA level remained below saturation level <6 mg/dL for more than 80% of the treatment period) and other 5 were considered partial responders, losing treatment efficacy due to immunogenicity to pegloticase and development of infusion reactions. Tophi volume before therapy was 9.15±13.26 cm^3 (mean±SD). After therapy, it reduced to 1.89+2.86 cm^3 (mean±SD). Responders presented a 94.76% volume reduction and in partial responders a 47.97% reduction was found. This study showed that the reduction of uric acid levels by pegloticase effectively and rapidly resolves tophi in the musculoskeletal tissues of patients with advanced gout.

Safety

The most common AEs observed with pegloticase were gout flares and infusion reactions.

In the first phase I trial, induration and mild to moderate pain at the injection site occurred in 6 patients, within a few hours of subcutaneous injection of pegloticase, resolving within 24–48 hours. Five of the 13 subjects developed antibodies anti-pegloticase. Interestingly, pUox declined faster in these patients and some of them developed hypersensitivity reactions.[19]

Twenty-two patients (92%) from the second phase I trial experienced AEs of mild to moderate severity. Acute gout flares were the most common. Other AEs in the study group included elevated blood pressure, dizziness, back pain, diarrhea, dyspepsia, and insomnia. In contrast with the previous trial, none of the patients experienced an infusion reaction. No relationship was observed between pegloticase dose and the risk of an AE. Nine patients developed antibodies to pegloticase following infusion and, again, there was evidence of immune mediated clearance of the drug.[20]

In the phase II trial, 93% of the patients reported AEs and their incidence was similar across all treatment regimens. The most common AEs were nephrolithiasis (15% of the subjects) and arthralgia (12%). Most AEs were considered to be unrelated to the study treatment (60%) and mild or moderate in severity (93%). There were 13 serious AEs, reported in 9 patients. Five of these (anemia, hypersensitivity, infected tophus, and gout flares [2 patients]) were considered to be possibly or probably related to the study drug, and 2 of them led to discontinuation of the treatment (infected tophus and hypersensitivity). Infusion-day AEs occurred in 18 patients, and constituted the main reason for study withdrawal (12 out

of 13 withdrawals). The most common were muscle spasm, dyspnea, and hypersensitivity. No anaphylactic reactions were observed but one case of hypersensitivity was reported as a serious AE. Antibodies against pegloticase were reported in 31 patients (76%). These patients did not suffer allergic reactions; however, half-life of pegloticase was shorter and the rate of non-responders was higher among them.[21]

More than 90% of the patients experienced AEs in the replicate RCTs. Serious AEs were more frequent in patients treated with biweekly (24%; 95% CI: 15–34) and monthly pegloticase (23%; 95% CI: 14–33) than in patients receiving placebo (12%; 95% CI: 4–25). The most common AE was gout flare, reported in approximately 80% of patients across the 3 pooled study groups. Although all patients, in the phase III studies, received anti-histamines and corticosteroids before the infusion, IR was the second most common AE. This was reported in 26% of patients receiving biweekly pegloticase, 42% of patients receiving monthly pegloticase, and 5% of patients receiving placebo.[20] In the OLE, IRs were observed in 44% of patients.[23] A more detailed analysis of IRs was published separately, combining data from both the RCTs and the OLE study.[28] In the pooled analysis, IRs were reported for 94 (45%) of 208 patients treated with pegloticase. The most common IRs were chest discomfort (15%), flushing (12%), dyspnea (11%), back pain (9%), hyperhidrosis (9%), nausea (9%), erythema (9%), urticaria (8%), chest pain (8%), pruritus (8%), rash (6%), muscle spasms (6%), headache (6%), and abdominal pain (5%). Although most IRs were rated mild or moderate in severity, 12 (7%) of 169 patients who started pegloticase during the RCTs and 11 (7%) of 149 patients who received pegloticase in the OLE experienced serious adverse reactions. IR was the basis for discontinuation from study drug for 20 patients in the RCTs and for 11 patients in the OLE study. Fortunately, all IRs resolved with supportive measures.[28]

Most IRs (91%) occurred in patients with pre-infusion serum uric acid concentrations >6 mg/dL. For patients sustaining pre-infusion serum urate <6 mg/dL, IRs occurred in fewer than 1 per 100 infusions. Therefore, IRs are associated with reduced urate-lowering efficacy, probably in patients who develop antibodies against pegloticase. Data from the RCTs revealed that 89% of patients treated presented antibodies against pegloticase.

Seven deaths (4 in the pegloticase group and 3 in the placebo group) occurred between randomization for RCTs and closure of the study period. Two deaths during the treatment period were attributed to cardiovascular AEs (cardiac arrest and arrhythmia), in the biweekly pegloticase group, in patients with previous cardiovascular risk factors at baseline.[22]

Discussion

In patients with refractory gout, pegloticase demonstrated fast and effective reduction of plasma urate levels, leading to reduced frequency of acute flares after 3 months of treatment (there are actually more flares during the first months), and tophi resolution. It was the first treatment for chronic gout demonstrating effectiveness in improving HRQoL and physical function. However, an important proportion of patients develops antibodies against pegloticase, after the first few infusions, resulting in reduced urate-lowering efficacy and the development of adverse reactions.

Confirming the potential benefits of the treatment with pegloticase, a recently published case report described the case of a nonagenarian with severe refractory tophaceous gout, resulting in functional impairment and loss of autonomy. The patient was treated with twice-monthly pegloticase infusions for 6 months, resulting in almost complete resolution of tophi and healing of skin erosions associated with them, leading to recovery of the patient's independence.[29]

Pegloticase appears to be, indeed, a valuable alternative for patients with severe gout who are non-responsive or intolerant to other ULTs, having proven its efficacy in several patient outcomes. However, some concerns remain about cost and safety issues.

Gout flares are frequent in the beginning of treatment, especially during the first 3 months of therapy; its occurrence seems to be more frequent than with oral ULT agents, which, in fact, can be explained by the greater urate-lowering capacity of pegloticase. Flare prophylaxis, as recommended by international guidelines,[7] may be insufficient in these patients. Perhaps a more aggressive prophylaxis with colchicine, NSAIDs, and/or corticosteroids, as proposed recently by Pascual et al,[30] should be adopted.

The risk of cardiovascular events is high among patients treated with pegloticase; this was identified as a trend in the RCTs[22] and confirmed in a nationwide database analysis.[28] Data are not conclusive on whether the higher frequency of cardiovascular events is due to treatment itself, to high doses of corticosteroids used to prevent gout flares, or to the high baseline cardiovascular risk of the patients eligible to treatment.

Immunogenicity remains the most relevant issue concerning drug safety and withdrawal. Anti-pegloticase antibodies can be identified in a significant percentage of patients and, in high titers, are responsible for a high risk of infusion reactions

and loss of efficacy.[31,32] The loss of efficacy of pegloticase, translated as pUAc >6 mg/dL, was a good surrogate marker for the presence of high titers of anti-pegloticase antibodies and, consequently, helpful to predict the occurrence of further infusion reactions. These findings led to the recommendation that the drug should be discontinued in patients with 2 sequential determinations of pUAc >6 mg/dL.[27] In addition, in a trial by Hershfield et al,[25] including 7 patients who were organ transplant recipients under immunosuppressive therapy, anti-plegloticase antibodies were found in only 1 of such patients; this finding unveils a possible role for concurrent immunosuppressive agents as a strategy to reduce antidrug antibody formation and thus avoid infusion reactions and loss of efficacy.

Finally, one major consideration to be held is that pegloticase trials took place before febuxostat and lesinurad were widely available (approved by FDA in 2009 and 2015, respectively), thus overestimating the number of patients who would benefit from the drug, since febuxostat came up as a valid and less expensive option for patients in whom allopurinol was contraindicated or uneffective[11,12,33,34] and lesinurad, in combination with the formerly mentioned therapies, demonstrated superior urate-lowering capacity to both drugs alone.[35,36] Considering costs and safety profile, pegloticase would eventually be the last resource for patients who are refractory to other available drugs – alone or in combination.

Disclosure

The authors report no conflicts of interest in this work.

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